An Algorithm to Estimate Monotone Normal Means and its Application to Identify the Minimum Effective Dose

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Abstract

In the standard setting of one-way ANOVA with normal errors, a new algorithm, called the Step Down Maximum Mean Selection Algorithm (SDMMSA), is proposed to estimate the treatment means under an assumption that the treatment mean is nondecreasing in the factor level. We prove that i) the SDMMSA and the Pooled Adjacent Violator Algorithm (PAVA), a widely used algorithm in many problems, generate the same estimators for normal means, ii) the estimators are the mle's, and iii) the distribution of each of the estimators is stochastically nondecreasing in each of the treatment means. As an application of this stochastic ordering, a sequence of null hypotheses to identify the minimum effective dose (MED) is formulated under the assumption of monotone treatment(dose) means. A step-up testing procedure, which controls

the experimentwise error rate in the strong sense, is constructed. When the MED=1, the proposed test is uniformly more powerful than Hsu and Berger's (1999).

Some key words: Closed test method; Experimentwise error rate; Maximum likelihood estimator; Step-up tests.

1 Introduction.

A situation frequently encountered in dose-response studies is identifying the minimum effective dose (MED). The MED is defined as the lowest dose such that the mean response is better than that of a zero-dose control by a clinically significant difference. Finding the MED is important since high doses often turn out to have undesirable side effects.

Consider the one-way layout model

$$Y_{ij} = \mu_i + \varepsilon_{ij} \tag{1.1}$$

for $i = 0, ..., k, j = 1, ..., n_i$, where μ_i's are the unknown response means at different dose levels and $\varepsilon_{ij} \sim N(0, \sigma^2)$ are the independent errors with an unknown variance. The parameter space is

$$H = \{\underline{\mu} = (\mu_0, \mu_1, ..., \mu_k) : \mu_1 \leq ... \leq \mu_k\} \tag{1.2}$$

(here, for simplicity, we omit σ in H), and the sufficient statistics are the sample means, $\bar{Y}_i$, and the mean squared error, denoted by S^2. Assume $i = 0$ is the control group. One goal is to find the smallest positive integer N satisfying $\mu_N > \mu_0 + \delta$ for a clinically significant difference constant $\delta \geq 0$. We call N the minimum effective dose (MED). Determination of the MED usually is done by step-down test procedures, see Williams (1971), Ruberg (1989), Tamhane, Hochberg, and Dunnett (1996), Hsu and Berger (1999), and Hellmich and Lehmacher (2005), among others. Tamhane,

Hochberg and Dunnett (1996) indeed proposed a step-up procedure SU1P to identify the MED. The SU1P procedure is based on the step-up procedure of Dunnett and Tamhane (1992), which controls the experimentwise error rate only for balanced designs. However, Dunnett and Tamhane (1995)'s step-up procedure for unbalanced designs case cannot control the experimentwise error rate. Liu (1997) proposed a method of calculating the critical values of the step-up procedure by Dunnett and Tamhane (1995). The SU1P procedure does not make use of the monotonicity, therefore its power should not be high. Intuitively it seems that step-down procedures infer a larger dose as the MED. Therefore, it is of interest to have a step-up procedure to use the monotonicity to increase its power.

To derive a test of level-α, one needs to find an appropriate statistic and its least favorable distribution in the null hypothesis. Thus a stochastic ordering for the test statistic is needed. The desired statistic, the estimator of μ_i, should be: a) nondecreasing in i, b) and is also nondecreasing in each of $\bar{Y}_j$'s. The PAVA algorithm generates the estimators that achieve a). However, it is difficult to show b) directly for these estimators using the PAVA. The PAVA was first proposed by Ayel, Brunk, Ewing, Reid and Silverman (1955), and was introduced to estimate the monotone proportions in independent binomial experiments. Surprisingly, it has many applications in normal, Poisson and multinomial distributions, etc. See more details in Robertson, Wright and Dykstra (1988). The PAVA is an iterative algorithm, each step is very simple to implement, however, it does not have a closed form for the final estimator. Hence, it is hard to establish analytic properties for the estimator. Notice these, a new algorithm, the SDMMSA, is proposed to overcome the drawbacks. We will show that the two algorithms yield the same estimators and each estimator is a monotone function of each $\bar{Y}_i$. The second fact is critical to determine the least favorable distribution in the null hypothesis space.

The rest of the article is organized as follows. Section 2 provides a new algorithm to generate estimators for μ_i's and discusses their analytic properties. In particular, a stochastic ordering for the distributions of the proposed estimators is established. In Section 3, one application of the stochastic ordering established in Section 2 is given to identify the MED. A step-up multiple test procedure that controls the experimentwise error rate in the strong sense is provided by constructing a sequence of increasing rejection regions of level-α for each null hypothesis in (3.25), and the proposed procedure is illustrated on a real data set. Section 4 concludes with some discussion.

2 A new algorithm to construct the estimator of μ_i and some analytic results.

In this section, an estimator of μ_i, denoted by $\hat{\mu}_i$, for any integer $i \in [1, k]$ under H is first constructed iteratively. Then three facts are established: $\hat{\mu}_i$ is the same as the estimator generated by the PAVA; $\hat{\mu}_i$ is the mle under H, and the distribution of $\hat{\mu}_i$ is stochastically non-decreasing in each μ_j.

2.1 A new iterative algorithm to construct $\hat{\mu}_i$.

Let

$$n_{i,j} = \sum_{h=i}^{j} n_h, \;\; \bar{Y}_{i,j} = \frac{\sum_{h=i}^{j} n_h \bar{Y}_h}{n_{i,j}}, \;\; \forall 1 \le i \le j \le k \tag{2.3}$$

be the sample size and the sample mean of a combined sample of treatments i through j, respectively.

Step 1). We construct $\hat{\mu}_i$ starting from $i = k$ using the data set $\{(\bar{Y}_i, n_i)\}_{i=1}^{k}$. Let

$$A_1 = \{j : \bar{Y}_{j,k} = max_{\{1 \le j' \le k\}}\{\bar{Y}_{j',k}\}\} \tag{2.4}$$

be a subset of $\{1, ..., k\}$(A_1 contains a single element with probability one), and let

$$i_1 = min\{A_1\}. \tag{2.5}$$

Then

$$\hat{\mu}_i \overset{def}{=} \bar{Y}_{i_1,k}, \ \ \forall \ i \in [i_1, k]. \tag{2.6}$$

If $i_1 = 1$, then all $\hat{\mu}_i$'s are defined and stop; otherwise go to the next step. Step 2). Note in this step $i_1 - 1 \leq k - 1$. Repeat Step 1 but using the data set $\{(\bar{Y}_i, n_i)\}_{i=1}^{i_1-1}$. i.e., let

$$A_2 = \{j : \bar{Y}_{j,i_1-1} = max_{\{1 \leq j' \leq i_1-1\}}\{\bar{Y}_{j',i_1-1}\}\} \tag{2.7}$$

be a subset of $\{1, ..., i_1 - 1\}$, and let

$$i_2 = min\{A_2\}. \tag{2.8}$$

Then

$$\hat{\mu}_i \overset{def}{=} \bar{Y}_{i_2,i_1-1}, \ \ \forall \ i \in [i_2, i_1 - 1]. \tag{2.9}$$

If $i_2 = 1$, then all $\hat{\mu}_i$'s are defined and stop; otherwise repeat this process for a number of times, say h times, until $i_h = 1$. Such an integer h exists, because i_j strictly decreases in j. Since $i_h = 1$, then all $\hat{\mu}_i$'s are defined and the construction on $\hat{\mu}_i$'s is complete. We name this the step-down-maximum-mean-selection algorithm (SDMMSA).

Remark 1. There exists partition, $\cup_{u=1}^{h}[i_u, i_{u-1} - 1]$, for $\{1, ..., k\}$ with $i_0 - 1 \overset{def}{=} k$. Following the construction of $\hat{\mu}_i$, each $\hat{\mu}_i$ is the sample mean of a combined sample of treatment(s) belonging to the interval in the partition that includes treatment i. Also $\hat{\mu}_i$ is constant in i on each integer interval $[i_u, i_{u-1} - 1]$ for $u = 1, ...h$, as shown in (2.6) and (2.9), and $\hat{\mu}_i$ is strictly increasing when i moves from $[i_u, i_{u-1} - 1]$ to $[i_{u'}, i_{u'-1} - 1]$ for $u > u'$, as shown in (2.4) and (2.7). Therefore, $\hat{\mu}_i$ is nondecreasing in i for $i \in [1, k]$. $\square$

Lemma 1 *For partition $\cup_{u=1}^{h}[i_u, i_{u-1} - 1]$ given in Remark 1, $\bar{Y}_{i_u-1} < \bar{Y}_{i_u}$ for any $u \in [1, h]$.*

Proof. Since the SDMMSA repeats itself in each step, without loss of generality, we only need to prove Lemma 1 for $u = 1$. i.e., $\bar{Y}_{i_1-1} < \bar{Y}_{i_1}$.

Suppose this is not true, i.e., $\bar{Y}_{i_1} \leq \bar{Y}_{i_1-1}$. Note $\bar{Y}_{i_1,k} \geq \bar{Y}_{i_1+1,k}$ by the definition of i_1, then

$$\bar{Y}_{i_1} \geq \bar{Y}_{i_1+1,k}. \tag{2.10}$$

Similarly, $\bar{Y}_{i_1-1} < \bar{Y}_{i_1,k}$ is true due to $\bar{Y}_{i_1-1,k} < \bar{Y}_{i_1,k}$. Therefore, $\bar{Y}_{i_1} \leq \bar{Y}_{i_1-1} < \bar{Y}_{i_1,k}$, which implies

$$\bar{Y}_{i_1} < \bar{Y}_{i_1+1,k},$$

a contradiction to (2.10). $\square$

Remark 2. If $\bar{Y}_i$ is nondecreasing in $i \in [1, k]$, then the partition, $\cup_{u=1}^{h}[i_u, i_{u-1} - 1]$, for $\{1, ..., k\}$ given in Remark 1 satisfies i) $\bar{Y}_i$ is constant when $i \in [i_u, i_{u-1} - 1]$, and ii) is strictly increasing when i moves from $[i_u, i_{u-1} - 1]$ to $[i_{u'}, i_{u'-1} - 1]$ for $u > u'$. Therefore, $\hat{\mu}_i = \bar{Y}_i$ for $i \in [1, k]$. $\square$

Example 1. Consider the data in Table 1, taken from Ruberg (1995). There are nine ($k = 9$) active dose groups and a zero dose control group with six ($n_i = 6, i = 0, ..., 9$) animals/group in the experiment. Following Step 1, we obtain $i_1 = 9$ and then $\hat{\mu}_9 = \bar{Y}_9$; following Step 2, we obtain $i_2 = 6$, then $\hat{\mu}_8 = \hat{\mu}_7 = \hat{\mu}_6$ and is equal to $\bar{Y}_{6,8} = 73.77$, the sample mean of the combined sample for $i = 8, 7, 6$. The construction of all $\hat{\mu}_i$'s ends at Step 7(=h) and their values are reported in Table 1. The partition given in Remark 1 is now

$$[9] \cup [6, 8] \cup [5] \cup [4] \cup [3] \cup [2] \cup [1],$$

with a notation of $[i] = [i, i]$. $\square$

2.2 The relationship between $\hat{\mu}_i$, $\hat{\mu}_i^{mle}$ and $\hat{\mu}_i^{pava}$.

So far, the estimator of μ_i under H typically is obtained following the pooled-adjacent-violators algorithm(PAVA, described later), for example, see Barlow, Bartholomew, Bremner and Brunk (1972), Robertson, Wright, and Dykstra (1988), and Silvapulle and Sen (2005). Denote this estimator by $\hat{\mu}_i^{pava}$. Now we show that $\hat{\mu}_i^{mle} = \hat{\mu}_i = \hat{\mu}_i^{pava}$ in Theorem 1 and Theorem 2 below.

Theorem 1 *Let $\hat{\mu}_i^{mle}$ be the maximum likelihood estimator for μ_i under H. Then $\hat{\mu}_i = \hat{\mu}_i^{mle}, \forall i \in [1, k]$. Therefore, $\hat{\mu}_i = \hat{\mu}_i^{mle}, \forall i \in [1, k]$.*

Proof of Theorem 1. Taking the log transformation on the joint pdf of Y_{ij}, it is easy to see that $\hat{\mu}_i^{mle}$ minimizes

$$f(\mu_1, ..., \mu_k) = \sum_{i=1}^{k} n_i(\bar{Y}_i - \mu_i)^2 = \sum_{u=1}^{h}[\sum_{j=i_u}^{i_{u-1}-1} n_j(\bar{Y}_j - \mu_j)^2] \stackrel{def}{=} \sum_{u=1}^{h} f_i(\mu_1, ..., \mu_k)$$

under H, where the intervals $[i_u, i_{u-1} - 1]$ for $u = 1, ..., h$ are given in Remark 1.

Now focus on each f_i. Without loss of generality, focus on f_1, then

$$f_1(\mu_1, ..., \mu_k) = \sum_{j=i_1}^{k} n_j(\bar{Y}_j - \mu_j)^2 = \sum_{j=i_1}^{k} n_i[(\bar{Y}_j - \hat{\mu}_j)^2 + 2(\bar{Y}_j - \hat{\mu}_j)(\hat{\mu}_j - \mu_j) + (\hat{\mu}_j - \mu_j)^2].$$

Rearrange the terms above and note $\hat{\mu}_j = \bar{Y}_{i_1,k}$ for $j \in [i_1, k]$, then

$$f_1(\mu_1, ..., \mu_k) = \{\sum_{j=i_1}^{k} n_j[(\bar{Y}_j - \hat{\mu}_j)^2 + (\hat{\mu}_j - \mu_j)^2]\} + 2\sum_{j=i_1}^{k} n_j(\bar{Y}_j - \hat{\mu}_j)(-\mu_j) \stackrel{def}{=} I_1 + I_2.$$

It is obvious that I_1 is minimized at $\mu_j = \hat{\mu}_j$ for $j \in [i_1, k]$; for I_2, apply Abel's partial summation formula and obtain

$$I_2 = 2\sum_{j=k}^{i_1} n_j(\hat{\mu}_j - \bar{Y}_j)\mu_j = 2\sum_{j=k}^{i_1+1} d_j(\mu_j - \mu_{j-1}) + d_{i_1}\mu_{i_1} = 2\sum_{j=k}^{i_1+1} d_j(\mu_j - \mu_{j-1}),$$

where $d_j = \sum_{v=k}^{j} n_v(\hat{\mu}_v - \bar{Y}_v) \geq 0$ and $d_{i_1} = 0$ due to the definition of i_1. Also note $\mu_j \geq \mu_{j-1}$. Thus I_2 is nonnegative and achieves its minimum at $\mu_{i_1} = ... = \mu_k$.

Therefore, combining I_1 and I_2, we conclude $f_1(\mu_1, ..., \mu_k)$ is minimized at $\mu_j = \hat{\mu}_j$ for $j \in [i_1, k]$.

Repeat the same argument on f_2 through f_h, each f_u is minimized at $\mu_j = \hat{\mu}_j$ for $j \in [i_u, i_{u-1} - 1]$. Lastly, note $\hat{\mu}_j$ nondecreasing, we conclude $\hat{\mu}_j^{mle} = \hat{\mu}_j$ for any $j \in [1, k]$. $\square$

Theorem 2 *For any* $i \in [1, k]$,

$$\hat{\mu}_i(\bar{Y}_1, ..., \bar{Y}_k) = \hat{\mu}_i^{pava}(\bar{Y}_1, ..., \bar{Y}_k). \tag{2.11}$$

For a data set of $\{(\bar{Y}_i, n_i)\}_{i=1}^k$, the PAVA proceeds as follows:

Step 0-PAVA). If $\bar{Y}_i$ is nondecreasing in i for $i \in [1, k]$, then $\hat{\mu}_i^{pava} = \bar{Y}_i$; otherwise, go to the next step.

Step 1-PAVA). Pick any consecutive pair $(\bar{Y}_j, \bar{Y}_{j+1})$ with $\bar{Y}_j > \bar{Y}_{j+1}$, let j_l be the smallest integer so that $\bar{Y}_i = \bar{Y}_j$ for $i \in [j_l, j]$ and let j_u be the largest integer so that $\bar{Y}_i = \bar{Y}_{j+1}$ for $i \in [j+1, j_u]$. For each $i \in [j_l, j_u]$, replace each $\bar{Y}_i$ by $\bar{Y}_{j_l, j_u}(= \frac{\sum_{i=j_l}^{j_u} n_i \bar{Y}_i}{\sum_{i=j_l}^{j_u} n_i})$, and then obtain a new data set of $\{(a_i, n_i)\}_{i=1}^k$, where $a_i = \bar{Y}_i$ for $i \notin [j_l, j_u]$ and $a_i = \bar{Y}_{j_l, j_u}$ for $i \in [j_l, j_u]$. Note two facts: $\bar{Y}_i$ is non-increasing for $i \in [j_l, j_u]$, and the number of different a_i's is strictly less than that of $\bar{Y}_i$'s.

Step 2-PAVA) Repeat this process on $\{(a_i, n_i)\}_{i=1}^k$ until all a_i's are nondecreasing. Then $\hat{\mu}_i^{pava} = a_i$. Since the number of different a_i's is strictly less than that in the previous step, this algorithm has to stop in a finite steps. $\square$

Proof of Theorem 2. When $\bar{Y}_i$ is nondecreasing in $i \in [1, k]$, then (2.11) is true due to Step 0-PAVA) and Remark 2. When $\bar{Y}_j > \bar{Y}_{j+1}$ for some j, let a_i and $[j_l, j_u]$ be given in Step 1-PAVA). It suffices to show

$$\hat{\mu}_i(\bar{Y}_1, ..., \bar{Y}_k) = \hat{\mu}_i(a_1, ..., a_k), \tag{2.12}$$

for any $i \in [1,k]$. Let $\cup_{u=1}^{h}[i_u, i_{u-1}-1]$ be the partition of $[1,k]$ given in Remark 1 using data $\{(\bar{Y}_i, n_i)\}_{i=1}^{k}$. The integer j_u has to belong to one of these intervals in the partition, say $[i_{u_j}, i_{u_j}-1]$. Since $\bar{Y}_i$ is non-increasing on $[j_l, j_u]$ as shown in Step 1-PAVA), by Lemma 1, $i_{u_j} \leq j_l$. Thus $[j_l, j_u]$ is a subset of $[i_{u_j}, i_{u_j}-1]$, an interval in the partition. Let $\cup_{u=1}^{h'}[i'_u, i'_{u-1}-1]$ be the partition of $[1,k]$ given in Remark 1 but using data $\{(a_i, n_i)\}_{i=1}^{k}$. Therefore, $[j_l, j_u]$ also has to be a subset of one of these intervals.

Case I). If $[j_l, j_u] \subset [i_1, k]$, i.e., $u_j = 1$, consider

$$a_{i,k} \stackrel{def}{=} \frac{\sum_{u=i}^{k} n_u a_u}{\sum_{u=i}^{k} n_u}$$

for $i \in [1,k]$. Note $a_{i,k} = \bar{Y}_{i,k}$ for $i \notin [j_l+1, j_u]$ and $i'_1 \leq j_l$, then $i'_1 = i_1$. Therefore,

$$\hat{\mu}_i(\bar{Y}_1, ..., \bar{Y}_k) = \frac{\sum_{i=i_1}^{k} n_i \bar{Y}_i}{\sum_{i=i_1}^{k} n_i} = \frac{\sum_{i=i'_1}^{k} n_i a_i}{\sum_{i=i'_1}^{k} n_i} = \hat{\mu}_i(a_1, ..., a_k),$$

for any $i \in [i_1, k]$. For any $i < i_1$, since $\hat{\mu}_i$ only depends on $\bar{Y}_1$ through $\bar{Y}_{i_1-1}$(or a_1 through a_{i_1-1}) and $\bar{Y}_i = a_i$, we conclude (2.12).

Case II). If $[j_l, j_u] \subset [i_2, i_1-1]$, i.e., $u_j = 2$, we only need to show $i'_1 = i_1$. Then, similar to Case I) above, (2.12) is established. To prove $i'_1 = i_1$, first note

$$a_{i_1,k} = \bar{Y}_{i_1,k} \geq \bar{Y}_{u,k} = a_{u,k}$$

for any $u \geq i_1$. So

$$i'_1 \leq i_1 \tag{2.13}$$

by the definition of i'_1.

Suppose $i'_1 < i_1$, we will construct a contradiction. Note $i'_1 \notin (j_l, j_u]$ because a_i is non-increasing on $(j_l, j_u]$. Thus,

$$\bar{Y}_{i'_1,k} = a_{i'_1,k} \geq a_{i_1,k} = \bar{Y}_{i_1,k},$$

a contradiction with the definition of i_1. Hence $i'_1 \geq i_1$. Together with (2.13), we conclude $i'_1 = i_1$.

For the other cases of $u_j = 3, ..., h$, similar to Case II), we can show $i_u = i'_u$ for all $u = 2, ..., h$. Hence, $h' = h$ and two partitions, $\cup_{u=1}^{h}[i_u, i_{u-1} - 1]$ and $\cup_{u=1}^{h'}[i'_u, i'_{u-1} - 1]$ are identical. Also note that $[j_l, j_u]$ is contained in one interval $[i_{u_j}, i_{u_j - 1} - 1]$, (2.12) is established. $\square$

Remark 3. Although $\hat{\mu}_i$ and $\hat{\mu}_i^{pava}$ generated by two algorithms are identical, there are several advantages of the SDMMSA over the PAVA. First, it is clear from the SDMMSA that $\hat{\mu}_i$ is uniquely defined, but not clear for $\hat{\mu}_i^{pava}$ from the PAVA, since the latter needs to show $\hat{\mu}_i^{pava}$ must be the same no matter where to start the algorithm, which is not obvious at all. Secondly, $\hat{\mu}_j$ has a closed form, $\bar{Y}_{i_j, i_{j-1}-1}$, if $j \in [i_{j_0}, i_{j_0-1} - 1]$ for some j_0, where i_{j_0} is given in Remark 1, while $\hat{\mu}_i^{pava}$ does not. This fact is important for establishing the stochastic ordering of $\hat{\mu}_i$ as shown in the next section. Thirdly, it was mentioned, for example, in Robertson, Wright and Dykstra (1988, p.10) that $\hat{\mu}_i^{pava}$ is the mle. To the best knowledge of the authors, no rigorous proof has been given. With $\hat{\mu}_i$, we proved $\hat{\mu}_i = \hat{\mu}_i^{mle}$ and $\hat{\mu}_i = \hat{\mu}_i^{pava}$. Thus $\hat{\mu}_i^{pava} = \hat{\mu}_i^{mle}$. Lastly, regarding the computation, the SDMMSA is easier to code than the PAVA since at each step of the SDMMSA a certain number of the final estimators ($\hat{\mu}_i$) are defined. $\square$

2.3 A stochastic ordering of $\hat{\mu}_i$.

We provide another major result in this paper which establishes a stochastic ordering for each $\hat{\mu}_i$ in terms of each of μ_j's. Let

$$\hat{\mu}_{i,k} = \hat{\mu}_i(\bar{Y}_1, ..., \bar{Y}_k) \tag{2.14}$$

be the estimator of μ_i obtained from the sample $\{(\bar{Y}_i, n_i)\}_{i=1}^{k}$ following Steps 1 and 2 in Section 2.1. So the distribution of $\hat{\mu}_{i,k}$ depends on μ_1 through μ_k and σ.

Theorem 3 *For each i and j in $[1,k]$, $\hat{\mu}_{i,k}$, as a function of $\bar{Y}_j$, is nondecreasing when the other $\bar{Y}_{j'}$'s are held fixed. Therefore, $\hat{\mu}_{i,k}$ is stochastically nondecreasing in μ_j when the other $\mu_{j'}$'s are held fixed. i.e., $P(\hat{\mu}_{i,k} > x)$ is a nondecreasing function of μ_j for any real number x.*

Proof of Theorem 3. We will prove the monotonicity of $\hat{\mu}_{i,k}$ in each $\bar{Y}_j$ by induction on k.

First for the case of $k = 1$, $\hat{\mu}_{1,1} = \bar{Y}_1$ is nondecreasing in $\bar{Y}_1$.

Assume that, for the case of $k = m$, $\hat{\mu}_{i,m}$ is nondecreasing in $\bar{Y}_j$ for any i and j no larger than m. Now consider the case of $k = m+1$. Following Step 1, i_1 depends on k, so write it as $i_1(k)$, i.e., obtain $i_1(k)$ using $(\bar{Y}_1, n_1)$ through $(\bar{Y}_k, n_k)$. Claim

$$i_1(m+1) = \begin{cases} m+1, & \text{if } \bar{Y}_{m+1} > \hat{\mu}_{i_1(m),m}, \\ i_1(m), & \text{if } \bar{Y}_{m+1} \in (\hat{\mu}_{i_2(m),m}, \hat{\mu}_{i_1(m),m}], \\ \ldots & \\ i_j(m), & \text{if } \bar{Y}_{m+1} \in (\hat{\mu}_{i_{j+1}(m),m}, \hat{\mu}_{i_j(m),m}], \\ \ldots. & \\ i_h(m), & \text{if } \bar{Y}_{m+1} \le \hat{\mu}_{i_h(m),m}. \end{cases} \tag{2.15}$$

When $\bar{Y}_{m+1} > \hat{\mu}_{i_1(m),m} (= \hat{\mu}_{m,m})$, for any $j \in [1,m]$, note

$$\bar{Y}_{j,m+1} = \frac{n_{j,m}\bar{Y}_{j,m} + n_{m+1}\bar{Y}_{m+1}}{n_{j,m} + n_{m+1}} \le \frac{n_{j,m}\hat{\mu}_{m,m} + n_{m+1}\bar{Y}_{m+1}}{n_{j,m} + n_{m+1}} < \bar{Y}_{m+1},$$

then $i_1(m+1) = m+1$.

When $\bar{Y}_{m+1} \in (\hat{\mu}_{i_2(m),m}, \hat{\mu}_{i_1(m),m}] = (\bar{Y}_{i_2(m),i_1(m)-1}, \bar{Y}_{i_1(m),m}]$. i) For $j \in [i_1(m), m+1]$, note $n_{j,m+1} - n_{i_1(m),m+1} \le 0$, then

$$\begin{aligned} & \bar{Y}_{i_1(m),m+1} - \bar{Y}_{j,m+1} \\ = \; & \frac{n_{j,m+1}(n_{i_1(m),m}\bar{Y}_{i_1(m),m} + n_{m+1}\bar{Y}_{m+1}) - n_{i_1(m),m+1}(n_{j,m}\bar{Y}_{j,m} + n_{m+1}\bar{Y}_{m+1})}{n_{i_1(m),m+1}n_{j,m+1}} \\ = \; & \frac{n_{j,m+1}n_{i_1(m),m}\bar{Y}_{i_1(m),m} - n_{i_1(m),m+1}n_{j,m}\bar{Y}_{j,m} + (n_{j,m+1} - n_{i_1(m),m+1})n_{m+1}\bar{Y}_{m+1}}{n_{i_1(m),m+1}n_{j,m+1}} \\ \ge \; & \frac{n_{j,m+1}n_{i_1(m),m}\bar{Y}_{i_1(m),m} - n_{i_1(m),m+1}n_{j,m}\bar{Y}_{i_1(m),m} + (n_{j,m+1} - n_{i_1(m),m+1})n_{m+1}\bar{Y}_{i_1(m),m}}{n_{i_1(m),m+1}n_{j,m+1}} \\ = \; & 0, \end{aligned}$$

and conclude $i_1(m+1) \leq i_1(m)$.

ii) For $j \in [1, i_1(m)-1]$, note

$$\bar{Y}_{j,m+1} = \frac{n_{j,i_1(m)-1}\bar{Y}_{j,i_1(m)-1} + n_{i_1(m),m}\bar{Y}_{i_1(m),m} + n_{m+1}\bar{Y}_{m+1}}{n_{j,m+1}},$$

and $\bar{Y}_{j,i_1(m)-1} \leq \bar{Y}_{i_2(m),i_1(m)-1} < \bar{Y}_{m+1}$, then

$$\begin{aligned} & \bar{Y}_{i_1(m),m+1} - \bar{Y}_{j,m+1} \\ = \; & \frac{n_{j,i_1(m)-1}n_{i_1(m),m}\bar{Y}_{i_1(m),m} + n_{j,i_1(m)-1}n_{m+1}\bar{Y}_{m+1} - n_{j,i_1(m)-1}(n_{i_1(m),m} + n_{m+1})\bar{Y}_{j,i_1(m)-1}}{n_{i_1(m),m+1}n_{j,m+1}} \\ > \; & 0, \end{aligned}$$

and conclude $i_1(m+1) > i_1(m) - 1$. Therefore, combining i) and ii) we obtain $i_1(m+1) = i_1(m)$ when $\bar{Y}_{m+1} \in (\hat{\mu}_{i_2(m),m}, \hat{\mu}_{i_1(m),m}]$.

For the other cases of $\bar{Y}_{m+1}$, (2.15) can be established in a similar way. Therefore, we conclude that $\hat{\mu}_{i,m+1}$ depends on $\{(\bar{Y}_j, n_j)\}_{j=1}^{m+1}$ through $\{(\hat{\mu}_{j,m}, n_j)\}_{j=1}^{m}$ and $(\bar{Y}_{m+1}, n_{m+1})$. So write

$$\hat{\mu}_{i,m+1} = \hat{\mu}_{i,m+1}(\hat{\mu}_{1,m}, ..., \hat{\mu}_{m,m}, \bar{Y}_{m+1}). \tag{2.16}$$

Also write $\hat{\mu}_{i,m+1}$ as

$$\hat{\mu}_{i,m+1} = \hat{\mu}_{i,m+1}(\bar{Y}_j), \tag{2.17}$$

since the other $\bar{Y}_{j'}$ are fixed. We will use any one of the above two notations whenever it is convenient. For $y < y'$, we need to show the monotonicity below

$$\hat{\mu}_{i,m+1}(y) \leq \hat{\mu}_{i,m+1}(y'), \tag{2.18}$$

which establishes the theorem, in the following two cases.

Case 1: $j = m+1$. Since $\hat{\mu}_{j',m}$ does not involve $\bar{Y}_{m+1}$ for all $j' \leq m$, (2.18) changes to

$$\hat{\mu}_{i,m+1}(\hat{\mu}_{1,m}, ..., \hat{\mu}_{m,m}, y) \leq \hat{\mu}_{i,m+1}(\hat{\mu}_{1,m}, ..., \hat{\mu}_{m,m}, y'), \tag{2.19}$$

which is established in Lemma 2 by noting $\hat{\mu}_{i,m}$ is nondecreasing in $i \le m$. Case 2: $j < m+1$. Since $\hat{\mu}_{j',m}(y) \le \hat{\mu}_{j',m}(y')$ for all $j' \le m$ by the induction assumption on the case of $k = m$, (2.18) changes to

$$\hat{\mu}_{i,m+1}(\hat{\mu}_{1,m}(y), ..., \hat{\mu}_{m,m}(y), \bar{Y}_{m+1}) \le \hat{\mu}_{i,m+1}(\hat{\mu}_{1,m}(y'), ..., \hat{\mu}_{m,m}(y'), \bar{Y}_{m+1}), \qquad (2.20)$$

which is established in Lemma 3. Therefore, the proof of the monotonicity of $\hat{\mu}_{i,k}$ in each $\bar{Y}_j$ is complete.

Since $\bar{Y}_j$'s are independent random variables, and each is stochastically increasing in μ_j, $\hat{\mu}_{i,k}$, as a nondecreasing function of each $\bar{Y}_j$, is also stochastically nondecreasing in μ_j. See, for example, Alam and Rizvi (1966) or Lemma 2 in Wu and Wang (2007). The proof of Theorem 3 is complete. $\square$

Lemma 2 *Let $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y)$ be the estimator following Steps 1 and 2 on a date set $\{(\bar{Y}_v, n_v)\}_{v=1}^{m+1}$ with $\bar{Y}_{m+1} = y$. Then*

$$\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y) \le \hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y')$$

if $\bar{Y}_v$ is nondecreasing in $v \in [1, m]$ and $y < y'$.

Proof of Lemma 2. Now write $i_1(m+1)$ introduced in (2.15) as $i_1(y)$.

First note $i_1(y) \le i_1(y')$, which follows (2.15) and $y < y'$.

Secondly, claim

$$i_1(y) = min\{v \in [1, m+1] : \bar{Y}_v \ge \bar{Y}_{v,m+1}\} \overset{\text{denoted by}}{=} A. \qquad (2.21)$$

Note

$$\bar{Y}_{v,m+1} - \bar{Y}_{v+1,m+1} = \frac{n_v(\bar{Y}_v - \bar{Y}_{v,m+1})}{n_{v+1,m+1}} = \frac{n_v(\bar{Y}_v - \bar{Y}_{v+1,m+1})}{n_{v,m+1}}. \qquad (2.22)$$

Therefore, $\bar{Y}_{v,m+1}$ is nonincreasing in v when $v \ge A$. Hence $i_1(y) \le A$. It is obvious that $\bar{Y}_{A-1,m+1} < \bar{Y}_{A,m+1}$ following the first equality in (2.22). Since $\bar{Y}_v$ nondecreasing in $v \in [1, m]$, $\bar{Y}_{v,m+1}$ is nondecreasing in v when $v \le A-1$. Thus (2.21) is established.

Thirdly, a) when $i < i_1(y)$, both $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y)$ and $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y')$ are constructed based on $\{\bar{Y}_v\}_{v=1}^{i_1(y')-1}$, a subset of $\{\bar{Y}_v\}_{v=1}^{m}$ which is nondecreasing in v. Thus $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y) = \bar{Y}_i = \hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y')$ following Remark 2.

b) When $i \in [i_1(y), i_1(y') - 1]$, $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y) = \bar{Y}_{i_1(y),m+1}$ with $\bar{Y}_{m+1} = y$; while $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y') = \bar{Y}_i \geq \bar{Y}_{i_1(y),m+1}$ following (2.21) and $\bar{Y}_v$ nondecreasing in $v \in [1, m]$.

c) When $i \in [i_1(y'), m + 1]$, $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y) = \bar{Y}_{i_1(y),m+1}$ with $\bar{Y}_{m+1} = y$; while $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y') = \bar{Y}_{i_1(y'),m+1}$ with $\bar{Y}_{m+1} = y'$. Then $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y) < \hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, y')$ due to $i_1(y) \leq i_1(y')$, $\bar{Y}_v$ nondecreasing in $v \in [1, m]$, $y < y'$ and (2.21). The proof is complete. $\square$

Lemma 3 *Let $\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, \bar{Y}_{m+1})$ be the estimator following Steps 1 and 2 on a date set $\{(\bar{Y}_v, n_v)\}_{v=1}^{m+1}$. Then*

$$\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, \bar{Y}_{m+1}) \leq \hat{\mu}_{i,m+1}(\bar{Y}'_1, ..., \bar{Y}'_m, \bar{Y}_{m+1})$$

if $\bar{Y}_v$ and $\bar{Y}'_v$ are both nondecreasing and $\bar{Y}_v \leq \bar{Y}'_v$ for $v \in [1, m]$.

Proof of Lemma 3. Claim

$$\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_{v-1}, \bar{Y}_v, \bar{Y}_{v+1}.., \bar{Y}_m, \bar{Y}_{m+1}) \leq \hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_{v-1}, \bar{Y}'_v, \bar{Y}_{v+1}.., \bar{Y}_m, \bar{Y}_{m+1}) \tag{2.23}$$

for any $v \in [1, m]$ if $\bar{Y}_1 \leq ... \leq \bar{Y}_{v-1} \leq \bar{Y}_v \leq \bar{Y}'_v \leq \bar{Y}_{v+1} \leq ... \leq \bar{Y}_m$. If (2.23) is true, then

$$\hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_m, \bar{Y}_{m+1}) \leq \hat{\mu}_{i,m+1}(\bar{Y}_1, ..., \bar{Y}_{m-1}, \bar{Y}'_m, \bar{Y}_{m+1}) \leq ... \leq \hat{\mu}_{i,m+1}(\bar{Y}'_1, ..., \bar{Y}'_m, \bar{Y}_{m+1}).$$

To show (2.23), now write $i_1(m + 1)$ introduced in (2.15) as $i_1(\bar{Y}_v)$(note $i_1(y)$ introduced in the beginning of the proof of Lemma 2 has a different argument $y = \bar{Y}_{m+1}$). Following (2.21) and the second equality of (2.22), $i_1(\bar{Y}_v) \leq i_1(\bar{Y}'_v)$. Similar

to the proof of Lemma 2, (2.23) can be shown in three cases a) $i < i_1(y)$, b) $i \in [i_1(y), i_1(y') - 1]$ and c) $i \in [i_1(y'), m+1]$, and the proof is complete. $\square$

In short, in this section, we proposed the SDMMSA to generate estimators for monotone normal means, μ_i, proved that the SDMMSA and the PAVA are equivalent, both generate the mle's, and the distribution of the proposed estimator is stochastically nondecreasing when μ_i goes larger. The last is to be used to derive a test to detect the MED in the response-dose study as shown in the next section.

3 A step-up testing procedure to detect the MED.

Now return to the problem of finding the minimum effective dose(MED). First, we formulate this as a multiple test problem by proposing a sequence of decreasing null hypotheses. Then a general result that identifies the least favorable distribution is provided. Finally, a sequence of increasing rejection regions of level-α is constructed.

3.1 Motivation.

Let

$$X_i = \bar{Y}_i - \bar{Y}_0 \text{ and } \eta_i = \mu_i - \mu_0 \text{ for } i = 1, ..., k. \tag{3.24}$$

Since the MED is to be found, one should start the search from $i = 1$ instead of $i = k$. Therefore, a step-up procedure seems more reasonable than a step-down one. To establish $N = 1$, some authors (see, for example Hsu and Berger (1999)) compare $min\{X_j : j \geq 1\}$ with δ and claim $N = 1$ if $min\{X_j : j \geq 1\} - \delta$ is large in the unit of S. Roughly speaking, they use $min\{X_j : j \geq i\}$ to estimate η_i. This does not fully utilize the assumption of the monotonicity on means. So we propose using the maximum likelihood estimator of η_i, denoted by $\hat{\eta}_i \overset{def}{=} \hat{\mu}_i - \bar{Y}_0$, as a test statistic, where $\hat{\mu}_i$ is given by the SDMMSA in Section 2.1. If $\hat{\eta}_1 - \delta$ is larger than a multiple of S, then claim $N = 1$ and stop; otherwise compare $\hat{\eta}_2 - \delta$ with S. Repeat this process

until we find an N so that $\hat{\eta}_N - \delta$ is much larger than S. If no such N can be found, then the MED does not exist.

To identify N(MED), let

$$\mathcal{C} = \{H_{0i} = \{\eta_i \leq \delta\} : i \in [1, k]\} \tag{3.25}$$

be the set of null hypotheses of interest in this section. For each $i \geq 1$, the alternative H_{Ai} claims $\eta_i > \delta$. If a certain H_{Ai} is established, then $N \leq i$ due to the monotonicity in μ_i's for $i \geq 1$. Therefore, N should be equal to the smallest i so that H_{Ai} is true. For the strong control of the experimentwise error rate, it is clear that $H_{0i'}$ is a subset of H_{0i} if $i < i'$ due to the monotonicity(i.e., H_{0i} is decreasing). Therefore, $\mathcal{C}$ itself is closed under the operation of intersection. The closed test procedure (Marcus, Peritz and Gabriel, 1976) can be applied on $\mathcal{C}$ to construct a step-up testing procedure with the experimentwise error rate controlled at α in the strong sense (see, for example, Hochberg and Tamhane (1987) for a definition) as long as a level-α test is constructed for each H_{0i}. Let R_i be a rejection region for H_{0i} for any i between 1 and k. In order to strongly control the experimentwise error rate, as well as being powerful, region R_i should satisfy the following two properties:

$*$) R_i is of level α, i.e., $\sup_{\underline{\mu} \in H_{0i}} P_{\underline{\mu}}(R_i) = \alpha$.

$**$) R_i is increasing in i. i.e. $R_i \subset R_{i'}$ if $i < i'$. Thus $R_i = \cap_{\forall H_{0i'} \subset H_{0i}} R_{i'} = \cap_{i'=i}^{k} R_{i'}$.

If these two are satisfied, then the multiple tests, which assert H_{Ai} if and only if R_i occurs, strongly control the experimentwise error rate at level α, which is the main result of this section.

3.2 A general result.

Theorem 4 *Let $T(t_1, ..., t_k)$ and $g_i(t_1, ..., t_k)$ for $i = 1, ..., k$ be non-decreasing function for any t_i when the other t_j's are held constant. Also*

$$g_i(ct_1 + d, ..., ct_k + d) = cg_i(t_1, ..., t_k) + d \tag{3.26}$$

for any constants $c > 0$ and d. Then

$$f(\eta_1, ..., \eta_k, \sigma) \stackrel{def}{=} ET(\frac{g_1(\bar{Y}_1, ..., \bar{Y}_k) - \bar{Y}_0 - \delta}{S}, ..., \frac{g_k(\bar{Y}_1, ..., \bar{Y}_k) - \bar{Y}_0 - \delta}{S}) \qquad (3.27)$$

is nondecreasing in each η_i when the other η_j and σ are held constants.

Proof of Theorem 4. Due to (3.26), we assume $\bar{Y}_0$ has a mean 0 and $\bar{Y}_i$ has a mean $\eta_i(= \mu_i - \mu_0)$. Let $\phi(x)$ be the pdf of $N(0,1)$ and $g_\nu(y)$ be the pdf of a χ^2-distribution with $\nu = \sum_{i=0}^k n_i - (k+1)$ degrees of freedom. Then

$$f(\eta_1, ..., \eta_k, \sigma) = \int\int ET(\frac{g_1 - x\frac{\sigma}{\sqrt{n_0}} - \delta}{\sqrt{\frac{\sigma^2 y}{\nu}}}, ..., \frac{g_k - x\frac{\sigma}{\sqrt{n_0}} - \delta}{\sqrt{\frac{\sigma^2 y}{\nu}}})\phi(x)g_\nu(y)dxdy.$$

For each fixed x and y, let

$$T_{x,y}(\bar{Y}_1, ..., \bar{Y}_k) = T(\frac{g_1 - x\frac{\sigma}{\sqrt{n_0}} - \delta}{\sqrt{\frac{\sigma^2 y}{\nu}}}, ..., \frac{g_k - x\frac{\sigma}{\sqrt{n_0}} - \delta}{\sqrt{\frac{\sigma^2 y}{\nu}}}),$$

which is non-decreasing in each $\bar{Y}_i$ due to the monotonicity of T and g_i's. Therefore, the conditional distribution of $T_{x,y}$ for given x and y is stochastically nondecreasing in each η_i(see Lemma 2 in Wu and Wang (2007)). Hence its conditional expectation

$$ET_{x,y} = ET(\frac{g_1 - x\frac{\sigma}{\sqrt{n_0}} - \delta}{\sqrt{\frac{\sigma^2 y}{\nu}}}, ..., \frac{g_k - x\frac{\sigma}{\sqrt{n_0}} - \delta}{\sqrt{\frac{\sigma^2 y}{\nu}}}) \qquad (3.28)$$

is nondecreasing in each η_i. So is f, the integral of (3.28). $\square$

Remark 3. Each $g_i(\bar{Y}_1, ..., \bar{Y}_k) \stackrel{def}{=} \hat{\mu}_i$ satisfies (3.26) and is nondecreasing in each $\bar{Y}_j$. We will use this to construct step-up tests in the next section. $\square$

Remark 4. If define $g_i(\bar{Y}_1, ..., \bar{Y}_k) = \bar{Y}_i$ for $i \in [1, k]$ and a sequence of

$$T_j^{HB} = I_{\{min_{\{i\in[j,k]\}}\{(\bar{Y}_i - \bar{Y}_0 - \delta)/\sqrt{1/n_i + 1/n_0}\} > t_{\alpha,\nu}\}}, \qquad (3.29)$$

for $j \in [1, k]$, then g_i and T_j^{HB} satisfy the conditions of Theorem 4. Hsu and Berger's step-down tests (1999) claim N, the MED, to be j_0 if $T_{j_0}^{HB} = 1$ but $T_{j_0-1}^{HB} = 0$. $\square$

3.3 The construction of step-up tests

We first construct a rejection region R_i^I with level α for each individual H_{0i}.

Lemma 4 *For a constant c, let*

$$R_{i,c}^I = \{\frac{\hat{\mu}_i - \bar{Y}_0 - \delta}{S} > c\}. \tag{3.30}$$

Then

$$sup_{\underline{\boldsymbol{\mu}} \in H_{0i}} P_{\underline{\boldsymbol{\mu}}}(R_{i,c}^I) = P_{\underline{\boldsymbol{\mu}}_i}(R_{i,c}^I), \tag{3.31}$$

where $\underline{\boldsymbol{\mu}}_i = (\mu_0, \mu_1, ..., \mu_k)$ with $\mu_1 = ... = \mu_i = \mu_0 + \delta$ and $\mu_{i+1} = ... = \mu_k = +\infty$. Therefore, for any $\alpha \in (0,1)$, $R_{i,c}^I$, with $c = c_{i,\alpha}$, defines a level-α test for H_{0i}, where $c_{i,\alpha}$ is the solution of

$$P_{\underline{\boldsymbol{\mu}}_i}(R_{i,c}^I) = \alpha. \tag{3.32}$$

Proof of Lemma 4. Let $T = I_{R_{i,c}^I}$. Then Lemma 4 follows Theorem 4. □

Remark 5. $c_{1,\alpha} = t_{\alpha,\nu}\sqrt{1/n_1 + 1/n_0}$ due to $\hat{\mu}_1 = \bar{Y}_1$ when $\underline{\boldsymbol{\mu}} = \underline{\boldsymbol{\mu}}_1$. □

Region $R_{i,c}^I$ satisfies property *), but not property **) in Section 2. To obtain more powerful multiple tests, we propose

Theorem 5 *For any integer $i \in [1,k]$ and for a sequence of nonnegative constants c_1 through c_i, let*

$$R_{c_1,...,c_i} = \cup_{j=1}^i R_{j,c_j}^I = \cup_{j=1}^i \{\frac{\hat{\mu}_j - \bar{Y}_0 - \delta}{S} > c_j\}. \tag{3.33}$$

Then

$$sup_{\underline{\boldsymbol{\mu}} \in H_{0i}} P_{\underline{\boldsymbol{\mu}}}(R_{c_1,...,c_i}) = P_{\underline{\boldsymbol{\mu}}_i}(R_{c_1,...,c_i}). \tag{3.34}$$

Therefore, for any $\alpha \in (0,1)$, $R_{c_1,...,c_i}$, with $c_1 = c_{1,\alpha}$ given in Remark 5 and c_i determined iteratively by solving

$$P_{\underline{\boldsymbol{\mu}}_i}(R_{c_1,\ldots,c_i}) = \alpha, \tag{3.35}$$

for $i = 2, ..., k$, defines a level-α test for H_{0i}.

Proof of Theorem 5. Let $T = I_{R_{c_1,\ldots,c_i}}$. Then Theorem 5 follows Theorem 4. $\square$

Theorem 6 *Consider all hypotheses in $\mathcal{C}$ in (3.25) with the following testing procedure:*

$$\textit{assert } H_{Ai} \textit{ (or not } H_{0i}\textit{) if } R_i \stackrel{def}{=} R_{c_1,\ldots,c_i} \textit{ occurs} \tag{3.36}$$

for any fixed $\alpha \in (0,1)$. Then the experimentwise error rate is at most α. i.e., the probability of making at least one incorrect assertion is at most α.

Proof of Theorem 6. The proof is trivial if one notices that H_{0i} is decreasing in i, and R_i is of level-α and is increasing in i. Then Theorem 6 follows the closed test procedure by Marcus, Peritz and Gabriel (1976). $\square$

Remark 6. Region R_i is increasing in i. Then R_i satisfies properties *) and **). $\square$

Remark 7. When the design is balanced, region R_1 contains the set of $\{T_1^{HB} = 1\}$, on which Hsu and Berger's test (1999) claims the MED=1. Therefore, the proposed test is uniformly more powerful than Hsu and Berger's when the MED=1. $\square$

Example 1(continued). The sample standard deviation $S = 7.751$, $t_{0.05,50} = 1.676$. We compare the new step-up procedure with the step-up procedure SU1P, the step-down Williams procedure and step-down procedure SD1P in Tamhane et al (1996) and the DR method in Hsu and Berger (1999). For illustration, $\delta = 6.5$. From Table 1 in Dunnett and Tamhane (1992) we have the critical values for the step-up procedure SU1P $c_1 = 1.645, c_2 = 1.933, c_3 = 2.071, c_4 = 2.165, c_5 = 2.237, c_6 = 2.294, c_7 = 2.342, c_8 = 2.382$ (we treat $df = 50$ as $df = \infty$). The SU1P procedure infers $\widehat{MED} =$

5. The Williams procedure has the $\bar{t}$ statistics: $\bar{t}_1 = -1.810, \bar{t}_2 = -0.961, \bar{t}_3 = 0.313, \bar{t}_4 = 1.899, \bar{t}_5 = 5.788, \bar{t}_6 = \bar{t}_7 = \bar{t}_8 = 9.334, \bar{t}_9 = 9.877$. The Williams statistics are compared with the following critical values (taken from Williams (1971)) in a step-down manner: $c_1 = 1.675, c_2 = 1.755, c_3 = 1.780, c_4 = 1.790, c_5 = 1.795, c_6 = 1.800, c_7 = 1.805, c_8 = 1.805, c_9 = 1.810$.. The Williams procedure infers $\widehat{MED} = 4$. By simulation with 1,0000 repetition, the critical values of the new statistic are $c_1 = 0.968, c_2 = 1.022, c_3 = 1.046, c_4 = 1.046, c_5 = 1.034, c_6 = 1.043, c_7 = 1.044, c_8 = 1.047, c_9 = 1.030$, respectively. Also $(\hat{\mu}_i - \bar{Y}_0 - \delta)/S$ for $i = 1, 2, 3, 4$ given in (3.33) are -1.045, -0.555, 0.181, and 1.097, respectively. Thus the new step-up procedure concludes $\widehat{MED} = 4$. So does Hsu and Berger (1999)'s DR method.

4 Discussion.

In this paper, we propose an alternative, SDMMSA, for the widely used PAVA. Although the two are equivalent, the SDMMSA is important by itself since it is easily coded and is well defined. Also a stochastic ordering of the estimators for the monotone normal means is established based on the SDMMSA. As one of its applications, a step-up test procedure is proposed to identify the MED. It strongly controls the experimentwise error rate, and is powerful to detect the MED, especially when the true MED is small.

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References

[1] Alam, K. and Rizvi, M. H. (1966). Selection from multivariate normal populations. *Ann. Inst. Statist. Math.* **18** 307–318.

[2] Ayel, M., Brunk, H. D., Ewing, G. M., Reid, W. T., and Silverman, E. (1955). An empirical distribution function for sampling with incomplete information. *Ann. Math. Statist.* **26** 641-647.

[3] Barlow, R. E., Bartholomew, D. J., Bremner, J. M., and Brunk, H. D. (1972). *Statistical Inference Under Order Restrictions*. Wiley, London.

[4] Dunnett, C. W. and Tamhane, A.C. (1992). A Step-Up Multiple Test Procedure, *J. Amer. Statist. Assoc.* **87**, 162-170.

[5] Dunnett, C. W. and Tamhane, A. C. (1995). Step-Up Multiple Testing of Parameters With Unequally Correlated Estimates. *Biometrics* **51** 217-227.

[6] Hochberg, Y. and Tamhane, A. C. (1987). *Multiple comparison procedures*. Wiley, New York.

[7] Hellmich, M. and Lehmacher, W. (2005). Closure procedures for monotone bi-factorial dose-response designs. *Biometrics* **61** 269-276.

[8] Hsu, J. C. and Berger, R. L. (1999). Stepwise confidence intervals without multiplicity adjustment for dose-response and toxicity studies. *J. Amer. Statist. Assoc.* **94** 468-482.

[9] Liu, W. (1997). Some results on step-up tests for comparing treatments with a control in unbalanced one-way layouts. *Biometrics* **53** 1508-1512.

[10] Marcus, R., Peritz, E. and Gabriel, K. R. (1976). On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* **63** 655-660.

[11] Robertson, T., Wright, F.T., and Dykstra, R. L. (1988). Order Restricted Statistical Inference. Wiley, New York.

[12] Ruberg, S. J. (1995). Dose-response studies II, analysis and interpretation. *Journal of Biopharmaceutical Statistics* **5** 15-42.

[13] Silvapulle, M. J. and Sen, P. K. (2005). *Constrained Statistical Inference*. Wiley, New Jersey.

[14] Tamhane, A. C., Hochberg, Y., Dunnett, C. W. (1996). Multiple Test Procedures for Dose Finding. *Biometrics* **52** 21-37.

[15] Williams, D. A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27** 103-117.

[16] Wu, S. S. and Wang, W. (2007). Step-up Simultaneous Tests for Identifying Active Effects in Orthogonal Saturated Designs. *Ann. Statist.* **35** 449-463.

TABLE 1. Sample dose-response data in Example 1

Dosage (mg/kg)	Sample size	Y_i	SD response	Index	$\hat{\mu}_i$	i_j
0	6	25.5	2.6	0	-	-
0.5	6	23.9	4.0	1	23.9	$i_7 = 1$
1.0	6	27.7	3.3	2	27.7	$i_6 = 2$
1.5	6	33.4	2.3	3	33.4	$i_5 = 3$
2.0	6	40.5	10.5	4	40.5	$i_4 = 4$
2.5	6	57.9	9.9	5	57.9	$i_3 = 5$
3.0	6	74.4	14.6	6	73.77	$i_2 = 6$
3.5	6	73.4	7.6	7	73.77	-
4.0	6	73.5	4.5	8	73.77	-
4.5	6	76.2	7.9	9	76.2	$i_1 = 9$